JAMA | Review

Fluid Therapy for Critically Ill Adults With Sepsis
A Review

Fernando G. Zampieri, MD, PhD; Sean M. Bagshaw, MD, MSc; Matthew W. Semler, MD, MSc

IMPORTANCE Approximately 20% to 30% of patients admitted to an intensive care unit have sepsis. While fluid therapy typically begins in the emergency department, intravenous fluids in the intensive care unit are an essential component of therapy for sepsis.

OBSERVATIONS For patients with sepsis, intravenous fluid can increase cardiac output and blood pressure, maintain or increase intravascular fluid volume, and deliver medications. Fluid therapy can be conceptualized as 4 overlapping phases from early illness through resolution of sepsis: resuscitation (rapid fluid administered to restore perfusion); optimization (the risks and benefits of additional fluids to treat shock and ensure organ perfusion are evaluated); stabilization (fluid therapy is used only when there is a signal of fluid responsiveness); and evacuation (excess fluid accumulated during treatment of critical illness is eliminated). Among 3723 patients with sepsis who received 1 to 2 L of fluid, 3 randomized clinical trials (RCTs) reported that goal-directed therapy administering fluid boluses to attain a central venous pressure of 8 to 12 mm Hg, vasopressors to attain a mean arterial blood pressure of 65 to 90 mm Hg, and red blood cell transfusions or inotropes to attain a central venous oxygen saturation of at least 70% did not decrease mortality compared with unstructured clinical care (24.9% vs 25.4%; $P = .68$). Among 1563 patients with sepsis and hypotension who received 1 L of fluid, an RCT reported that favoring vasopressor treatment did not improve mortality compared with further fluid administration (14.0% vs 14.9%; $P = .61$). Another RCT reported that among 1554 patients in the intensive care unit with septic shock treated with at least 1 L of fluid compared with more liberal fluid administration, restricting fluid administration in the absence of severe hypoperfusion did not reduce mortality (42.3% vs 42.1%; $P = .96$). An RCT of 1000 patients with acute respiratory distress during the evacuation phase reported that limiting fluid administration and administering diuretics improved the number of days alive without mechanical ventilation compared with fluid treatment to attain higher intracardiac pressure (14.6 vs 12.1 days; $P < .001$), and it reported that hydroxyethyl starch significantly increased the incidence of kidney replacement therapy compared with saline (7.0% vs 5.8%; $P = .04$), Ringer lactate, or Ringer acetate.

CONCLUSIONS AND RELEVANCE Fluids are an important component of treating patients who are critically ill with sepsis. Although optimal fluid management in patients with sepsis remains uncertain, clinicians should consider the risks and benefits of fluid administration in each phase of critical illness, avoid use of hydroxyethyl starch, and facilitate fluid removal for patients recovering from acute respiratory distress syndrome.

JAMA. 2023;329(22):1967-1980. doi:10.1001/jama.2023.7560

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Section Editor: Mary McGrae McDermott, MD, Deputy Editor.

Approximately 20% to 30% of patients admitted to an intensive care unit (ICU) have sepsis.[1] Of these, approximately 25% to 40% die prior to hospital discharge.[2,3] Fluid therapy is an important component of treatment for patients with sepsis.[4,5] Fluid therapy may be administered during any phase of critical illness with sepsis, including before, during, and after ICU admission. This review summarizes fluid therapy in the ICU for patients critically ill with sepsis.

Methods

We searched PubMed for the terms *early goal-directed therapy* [and] *sepsis*, *fluid resuscitation* [and] *sepsis*, *fluid therapy* [and] *sepsis* [and] *critical illness*, *fluid responsiveness* [and] *sepsis*, and *POCUS* (point-of-care ultrasonography) [and] *critical care* for relevant references. Of 5585 manuscripts identified, 76 articles were

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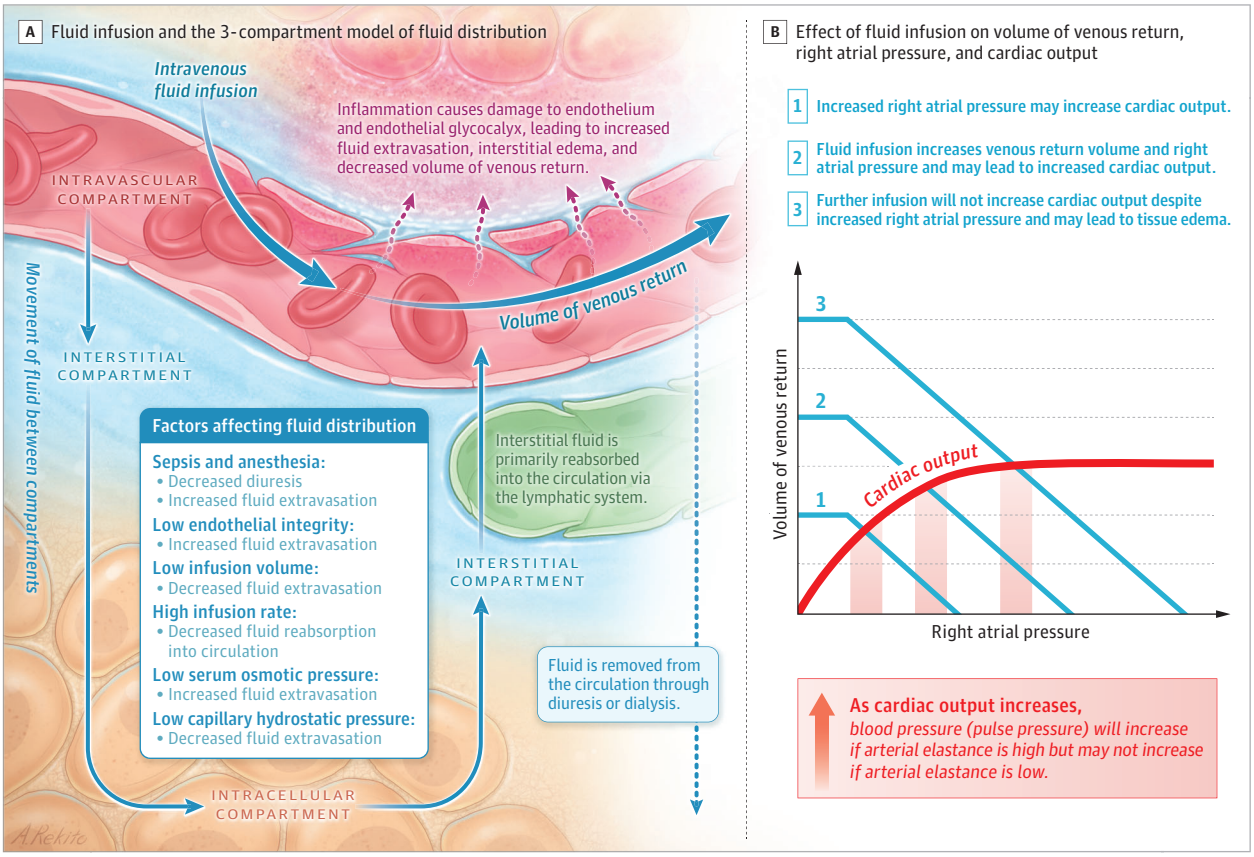
Figure 1. Fluid Infusion in Sepsis


A Fluid infusion and the 3-compartment model of fluid distribution
Intravenous fluid infusion
Inflammation causes damage to endothelium and endothelial glycocalyx, leading to increased fluid extravasation, interstitial edema, and decreased volume of venous return.
INTRAVASCULAR COMPARTMENT
Volume of venous return
Movement of fluid between compartments
INTERSTITIAL COMPARTMENT
Factors affecting fluid distribution
Sepsis and anesthesia:
• Decreased diuresis
• Increased fluid extravasation
Low endothelial integrity:
• Increased fluid extravasation
Low infusion volume:
• Decreased fluid extravasation
High infusion rate:
• Decreased fluid reabsorption into circulation
Low serum osmotic pressure:
• Increased fluid extravasation
Low capillary hydrostatic pressure:
• Decreased fluid extravasation
Interstitial fluid is primarily reabsorbed into the circulation via the lymphatic system.
INTERSTITIAL COMPARTMENT
Fluid is removed from the circulation through diuresis or dialysis.
INTRACELLULAR COMPARTMENT
B Effect of fluid infusion on volume of venous return, right atrial pressure, and cardiac output
1 Increased right atrial pressure may increase cardiac output.
2 Fluid infusion increases venous return volume and right atrial pressure and may lead to increased cardiac output.
3 Further infusion will not increase cardiac output despite increased right atrial pressure and may lead to tissue edema.
Volume of venous return
Cardiac output
Right atrial pressure
As cardiac output increases, blood pressure (pulse pressure) will increase if arterial elastance is high but may not increase if arterial elastance is low.

A, In the classic 3-compartment model, fluid administered intravenously distributes from the plasma to the interstitium and from the interstitium to cells. Filtered fluid returns to the plasma mostly through the lymph system and is eliminated by urine.[8,9] The composition of the fluid (ie, colloid vs crystalloid) and the characteristics of its administration (eg, volume and rate) influence its movement from the plasma into the interstitium and cells.[8] B, In the classic Frank-Starling model of cardiac physiology, when intravenous fluid administration increases intravascular volume, the volume of blood in the right ventricle increases. If the heart is in the ascending part of the curve, the increased ventricular filling increases cardiac output. If the heart is further to the right on the curve, further fluid administration may not increase cardiac output. Whether an increase in cardiac output increases arterial blood pressure depends on cardiac elastance.

included, consisting of 28 randomized clinical trials (RCTs), 7 secondary analyses of RCTs, 20 observational studies, 5 systematic reviews/meta-analyses, 1 scoping review, and 1 practice guideline. The remaining 14 references were added from reference review. RCTs, including relevant secondary analyses of clinical trial data, were prioritized for inclusion.

Pathophysiology of Fluid Therapy

Multiple physiological pathways responsible for maintaining intravascular volume, venous return, cardiac output, and tissue perfusion are disrupted by sepsis. Fluid losses, combined with increased venous capacitance and decreased venous resistance, reduce the effective intravascular volume in sepsis, which may decrease venous return, cardiac output, and tissue perfusion.[6,7] Intravenous (IV) fluid therapy can increase blood volume in the vasculature, the volume of venous blood returning to the heart, the cardiac output, and the volume of oxygen delivered to tissues (**Figure 1**).[8,10] Changes in arterial pressure after fluid administration depend on arterial elastance. A fluid bolus increases blood pressure by a greater amount when the arteries are stiff and noncompliant (high elastance) compared with when the arteries are flexible and compliant.[11] Therefore, fluid administration may increase a patient's cardiac output without increasing blood pressure.

Fluid Distribution

Administered fluid distributes initially to the intravascular compartment and then distributes to the interstitial and intracellular compartments.[8] Fluid influx into the interstitial compartment is primarily reabsorbed into the circulation through the lymphatic system.[9] Serum oncotic pressure, endothelial integrity, capillary hydrostatic pressure, fluid infusion rate and volume, and other factors affect fluid distribution.[8] While hemodynamic improvements (eg, augmented cardiac output, increased arterial blood pressure, and improved tissue perfusion) can occur during initial fluid therapy, excessive fluid administration can cause fluid extravasation and interstitial edema, especially in sepsis. Damage to the vascular endothelium and the endothelial glycocalyx in sepsis may increase fluid extravasation (Figure 1). Tissue edema due to increased venous pressure has been associated with organ dysfunction and potential complications[12] such as intra-abdominal hypertension

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and compartment syndrome.[13] Fluid therapy should be tailored to maximize early benefits while minimizing adverse effects.

Four Forms of Fluid Use

Critically ill patients primarily receive IV fluids in 4 forms: fluid challenge, fluid bolus, maintenance or replacement fluid or as part of parenteral nutrition, and medication diluent or carrier. A fluid challenge is the administration of a small volume of IV fluid (eg, 250 mL) over a short period (eg, 10 minutes) with the goal of assessing a patient's physiological response to the fluid such as changes in cardiac output, heart rate, arterial blood pressure, or urinary output.[14] A fluid bolus is the administration of a larger volume of IV fluid (eg, 500 mL or 1000 mL) over a relatively short period (eg, 15 minutes), with the goal of increasing intravascular volume. Maintenance or replacement fluid is the administration of IV fluid at lower rates over longer durations (eg, hours to days) with the aim of providing daily needs for water, electrolytes, nutrition, and replacement of measured losses (eg, urine, gastrointestinal, drains). Critically ill patients also receive substantial volumes of IV fluid as medication diluent or carrier, for which the goal is to facilitate the administration of medication. Accumulation of fluid administered is often an unintended adverse effect.[15]

Assessment for Fluid Therapy

Overview

Assessing whether IV fluid administration is indicated requires assessment of the patient's medical history, physical examination, laboratory evaluation, and diagnostic imaging (ie, chest radiograph to assess pulmonary edema or point-of-care ultrasound to assess the etiology of shock. Assessment of intravascular volume status and the expected response to IV fluid administration can be challenging.[4] Because markers of hypoperfusion (eg, altered mental status, low arterial pressure, cutaneous mottling, slow capillary refill time, low urine output, increased lactate) are not specific to hypovolemia, they must be considered in the clinical context of the patient and not as stand-alone indications for fluid therapy.

Assessment of Fluid Responsiveness

Scientific investigation has developed and validated objective measures to anticipate a patient's physiological response to an IV fluid bolus prior to fluid administration.[16-28] Each measure assesses cardiac preload to distinguish between patients for whom an IV fluid bolus would be anticipated to increase stroke volume (and cardiac output [termed *fluid responsive*]) from patients for whom an IV fluid bolus would not be anticipated to increase stroke volume (and cardiac output [termed *fluid nonresponsive*]) before fluid is administered to be patient. Approximately 57% of patients with sepsis are fluid responsive at presentation.[29] Patients with low variation in pulse pressure or stroke volume while receiving controlled mechanical ventilation or those who do not increase cardiac output after a passive leg raising maneuver (**Table 1**)[16-26] may be considered as fluid nonresponsive. These patients would not be expected to increase cardiac output in response to a fluid bolus. Dynamic measurements such as passive leg raising or pulse pressure variation, may identify patients who are fluid responsive more accurately than static measurements, such as measurement of central venous pressure.[27] An increase in cardiac output with passive leg raising identified patients whose cardiac output would increase with a fluid bolus (positive likelihood ratio, 11 [95% CI, 7.6-17]; specificity, 92%).[28] Lack of increase in cardiac output with passive leg raising identified patients whose cardiac output would not increase with a fluid bolus (negative likelihood ratio, 0.13 [95% CI, 0.07-0.22]; sensitivity of 88%).[28]

For each measure of fluid responsiveness, there are circumstances in which the measure is not valid or reliable (Table 1). Technical and operator-dependent factors may also affect accuracy and interpretation. Clinicians may select the most suitable method to evaluate fluid responsiveness according to patient characteristics and resource availability. Although withholding fluid therapy from patients expected to be fluid nonresponsive and administering fluid to patients who are expected to be fluid responsive is logical,[28] few data are available to inform whether this approach improves patient outcomes. Fluid responsiveness is not, when considered as an independent factor, a marker of need for fluid therapy in the absence of hypoperfusion.[30]

Role of Point-of-Care Ultrasonography

Point-of-care ultrasound refers to a directed ultrasound examination by the bedside clinician to evaluate for specific life-threatening abnormalities or diagnostic information. Point-of-care ultrasound can evaluate the etiology of shock and predict fluid responsiveness; it facilitates iterative assessment of cardiac function, characterizes preload responsiveness (eg, assessment of stroke volume changes during passive leg raising), and evaluates patients for complications of fluid accumulation (eg, assessing for lung edema[31] before administering fluid).

Evaluating inferior vena cava diameter combined with patterns of venous flow in liver and kidneys may identify tissue edema and inform the decision to continue or to withhold fluid therapy.[26] Abnormalities in flow pattern may differentiate simple fluid accumulation from organ dysfunction induced by increased systemic venous pressure. Point-of-care ultrasound may be limited by interoperator experience and variability, changes in assessment between spontaneous breathing and positive pressure ventilation, and other technical limitations.[26]

Fluid Therapy Goals

In addition to fluid therapy directed by fluid responsiveness, other end points for fluid therapy over the course of critical illness have been proposed such as lactate, capillary refill time, and central venous saturation (**Table 2**).[32-43] Despite significant research, optimal outcomes in response to fluid therapy for critically ill patients remain uncertain. Normalizing blood pressure is no longer considered a sufficient goal for resuscitation. Clinicians should select multiple therapeutic goals for each patient such as normalization of capillary refill time, lactate clearance, and normalization of urinary output.[27]

Administration of Fluid Therapy

Timing of Fluid Administration and Removal

Fluid therapy for sepsis occurs in 4 phases of critical illness: resuscitation, optimization, stabilization, and evacuation.[10] Each phase of therapy is associated with a separate clinical state of the patient,

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Table 1. Measures and Tests for Identifying Whether a Fluid Challenge Is Likely to Increase Cardiac Output

Marker	Definition	Normal range	Rationale	Comments and application	Application
Central venous pressure[16]	Estimates the right atrial pressure and cardiac preload	5-10 cm H_2O	Enables measuring vascular system pressure using centrally placed venous catheters to estimate stressed volume, defined as the volume in the vasculature that exerts stretch on vessel walls Low values imply patients may increase cardiac output and other hemodynamic parameters (eg, blood pressure) with fluid therapy	An isolated or static measure of central venous pressure alone may not reflect whether a patient will be responsive to fluid therapy	Measures should be integrated with additional clinical information and the broader context to inform the value of fluid therapy
Pulmonary artery occlusion pressure[16]	Estimates left ventricular end-diastolic pressure or left atrial pressure	4-12 cm H_2O	Enables measuring vascular system pressure using centrally placed venous catheters to estimate stressed volume, defined as the volume in the vasculature that exerts stretch on vessel walls Low values imply patients may increase cardiac output and other hemodynamic parameters (eg, blood pressure) with fluid therapy	An isolated or static measure of pulmonary artery occlusion pressure alone may not reflect whether a patient will be responsive to fluid therapy	Measures should be integrated with additional clinical information and the broader context to inform the value of fluid therapy
Pulse pressure variation[17-20a]	Indicates the change in pulse pressure that occurs during respiration with mechanical ventilation	10%-15%	Pulse pressure (systolic pressure minus diastolic pressure)[a] varies normally during the respiratory cycle in patients receiving mechanical (positive pressure) ventilation due to dynamic changes in intrathoracic pressure During positive pressure ventilation, a larger difference in pulse pressure between inspiration and expiration are associated with the following events: A decrease in right ventricular venous return leading to a decrease in left ventricular filling after a lag of 2-4 heartbeats An increase in cardiac preload and output with large pulse pressure variation in response to a fluid challenge	Conditions with which pulse pressure variation may be a less reliable predictor of fluid responsiveness: Spontaneous breathing (false positive) Cardiac arrhythmias (false positive) Increased intra-abdominal pressure (false positive) Right ventricular dysfunction (false positive) Low tidal volume or low compliance (false negative)	Pulse pressure variation >10%-12% has a sensitivity of 88% and a specificity of 89% for predicting fluid responsiveness Pulse pressure variation >10%-12% threshold would discriminate a greater likelihood of fluid responsiveness; however, different thresholds may be used in different conditions
Stroke volume variation[20,21b]	Indicates the dynamic change in left ventricular stroke volume occurring during respiration with mechanical ventilation	10%-13%	Large decreases in stroke volume between expiration and inspiration (>25%) among patients receiving positive pressure ventilation indicates decreased right ventricular preload and venous return and identifies patients who are more likely to experience increased cardiac preload and output in response to a fluid challenge	Similar to pulse pressure variation, there are conditions in which stroke volume variation may be a less reliable predictor of fluid responsiveness: Spontaneous breathing (false positive) Cardiac arrhythmias (false positive) Increased intra-abdominal pressure (false positive) Right ventricular dysfunction (false positive) Low tidal volume or low compliance (false negative)	A value of stroke volume variation >12% threshold may be used to predict fluid responsiveness Performance is similar to that of pulse pressure variation
End-expiratory occlusion test[22]	Indicates an approximate 15-s occlusion of the endotracheal tube in a patient receiving mechanical ventilation at end expiration	Variable	Large increases in pulse pressure (>15%) and cardiac output (>12%) following the end-expiratory occlusion test predict greater likelihood of responsiveness to a fluid challenge Temporarily augments venous return, cardiac preload, and stroke volume in responsive patients, mimicking as a fluid challenge	Like other dynamic maneuvers to predict fluid responsiveness, the end-expiratory occlusion test requires patients to receive invasive mechanical ventilation Conditions in which the end-expiratory occlusion test may be limited or a less reliable predictor of fluid responsiveness: Inability to perform a 15-s end-expiratory occlusion test in patients with spontaneous high work of breather Low tidal volume or low compliance (false negative)	A change in pulse pressure >5% during the end-expiratory occlusion test is associated with an increase in cardiac output with a fluid challenge with a sensitivity of 87% and a specificity of 100%

(continued)

goals of fluid therapy, assessments performed, and the interventions delivered (**Figure 2** and **Table 3**).[32,38,39,42,44-49] These phases highlight that the approach to fluid therapy changes during a patient's critical illness and recovery. This conceptual framework

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Table 1. Measures and Tests for Identifying Whether a Fluid Challenge Is Likely to Increase Cardiac Output (continued)

Marker	Definition	Normal range	Rationale	Comments and application	Application
Passive leg raising[20,23]	Indicates a dynamic maneuver to assess for changes in cardiac preload and output in response to rapid repositioning of a semirecumbent patient to supine with both legs raised to 30°-45°	Variable	Large increases in pulse pressure or stroke volume (>10%-15%) following a passive leg raising test predict greater likelihood of fluid responsiveness Passive leg raising can temporarily augment venous return, cardiac preload, and stroke volume in responsive patients, mimicking as a fluid challenge (≈300 mL of autotransfusion)	Unlike other dynamic maneuvers to predict fluid responsiveness, the passive leg raising test does not require a patient to receive invasive mechanical ventilation Conditions in which passive leg raising may not be feasible or is limited to predict fluid responsiveness: Severe hypovolemia (false negative) Raised intra-abdominal pressure (false negative) Inability to mobilize or to rapidly change position in bed (eg, spinal trauma) Diminished response with concomitant use of compression stockings May be influenced by operator, including correct passive leg raising technique, and cardiac output assessment	A change in stroke volume >9% and pulse pressure >10% during passive leg raising is associated with an increase in cardiac output with a fluid challenge with pooled sensitivity of 85% and a specificity of 91%
Mini fluid challenge[20,24]	Indicates a dynamic maneuver in which a small volume of fluid (≈ 100 mL) is given rapidly over ≈ 1 min to predict fluid responsiveness	Variable	Large increases (>10%) in velocity time index (an estimate of stroke volume) following a rapid 100-mL fluid bolus (followed by 400 mL over 14 min) is predictive of fluid responsiveness	Unlike other dynamic maneuvers to predict fluid responsiveness, the mini does not require a patient to be mechanically ventilated or to initially receive a large volume of fluid Added considerations in which the mini may be limited: Not well validated Requires administration of fluid bolus Requires point-of-care ultrasound to measure real-time change in velocity time index	A change in velocity time index >10% in response to a 100-mL fluid challenge is associated with an increase in cardiac output with a fluid challenge with a sensitivity of 95% and a specificity of 78%
Point-of-care ultrasound[25,26]	Indicates a directed ultrasound for several parameters to predict fluid responsiveness and assess for complications of fluid therapy	Variable	Estimates the following parameters: Subaortic velocity time index as an estimate of stroke volume Assesses left ventricular end-diastolic volume as an estimate of preload Assesses the inferior vena cava diameter and variation in inspiratory collapse to predict fluid responsiveness (or intolerance) Assesses lung parenchyma for pulmonary edema (eg, B-lines) to predict fluid intolerance	Advantages: Noninvasive Enables serial assessment Enables assessment for changes in response to interventions Contexts in which point-of-care ultrasound may be limited or less reliable: Operator training for image acquisition and interpretation Dynamic measures such as respiratory variation in inferior vena cava diameter is less reliable in patients receiving mechanical ventilation	Point-of-care ultrasound is a versatile tool that can inform both fluid responsiveness and fluid intolerance

Abbreviations: PPmax, maximum observed difference between systolic and diastolic pressure; PPmin, minimal difference between systolic and diastolic pressure during ventilatory cycle; SVmax, maximum observed difference between systolic and diastolic stroke volume; SVmin, minimal stroke volume observed during ventilatory cycle; SVmean, average stroke volume over the ventilatory cycle.

[a] The formula for pulse pressure variation: (PPmax – PPmin)/(PPmax + PPmin)/2.

[b] The formula for stroke volume variation (SVmax – SVmin)/(SVmean).

begins with rapid initial resuscitation, proceeds through optimization of organ and tissue perfusion, is followed by a phase of physiologic stabilization, and ends with a phase of recovery of organ dysfunction, often characterized by facilitated fluid evacuation.[10]

Resuscitation

In the resuscitation phase, the therapeutic goal is to rapidly reverse hypoperfusion, with or without hypotension, administering fluid boluses (and frequently administering vasopressors). Prior to fluid resuscitation, sepsis diagnosis and evidence of hypoperfusion should be established. Evidence of hypoperfusion includes altered level of consciousness, low arterial blood pressure (typically defined as a mean arterial pressure < 65 mm Hg), decreased urinary output (< 0.5 mL/kg/h), livedo reticularis, prolonged capillary refill time (≥ 3 seconds), and elevated serum lactate (> 2 mmol/L) (Table 2).

Assessments of fluid responsiveness and diagnostic evaluation of the cause of the hemodynamic abnormality occur in the

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Table 2. Summary of Measures to Guide Fluid Therapy in Patients With Sepsis

Measure	Definition	Normal range at rest	Rationale	Comments
Heart rate[32]	The number of heart beats/min	60-100 beats/min	When blood pressure is low, heart rate increases to increase cardiac output and delivery of oxygen Heart rate may return to normal when hypovolemia is corrected	Tachycardia may result from factors other than hypovolemia (eg, fever) or may not occur when hypovolemia is present (eg, after β-blocker receipt) Heart rate is not a sufficient measure to guide fluid therapy for most patients
Mean arterial blood pressure[33-35]	Average arterial pressure throughout 1 cardiac cycle	70-100 mm Hg	Mean arterial pressure is an assessment of perfusion of vital organs Perfusion of vital organs decreases with mean arterial pressures <60-65 mm Hg	Maintaining a mean arterial blood pressure ≥65 mm Hg is recommended for most critically ill adults with sepsis A low mean arterial pressure does not accurately identify patients whose cardiac output will increase with fluid administration
Cardiac output[36]	Volume of blood pumped by the heart/min	5-6 L/min	Cardiac output determines, in part, the volume of oxygen delivered to organs and tissues If cardiac output is insufficient to deliver adequate oxygen to tissues, ischemia and anaerobic metabolism occur	The balance of oxygen supply and demand is more important than absolute values for cardiac output Even with sufficient cardiac output, disordered microcirculation in sepsis may impair perfusion RCTs have not found that increasing cardiac output improves outcomes in sepsis
$ScvO_2$[32,37-39]	Hemoglobin saturation of blood in the superior vena cava	70%-80%	$ScvO_2$ reflects the balance between global oxygen delivery and global oxygen consumption Low values suggest that increasing the delivery of oxygen to tissues may be beneficial	RCTs did find using $ScvO_2$ to guide treatment to improve outcomes in sepsis Measuring $ScvO_2$ requires a central venous catheter Low values of $ScvO_2$ may identify patients with inadequate oxygen delivery, and high values may identify patients with impaired oxygen extraction
Central venous pressure[32,37-39]	Blood pressure in the vena cava near the right atrium	5-10 cm H_20	Central venous pressure has been used as a surrogate measure for right atrial pressure, right-ventricular end-diastolic pressure, and cardiac preload	Central venous pressure does not accurately identify patients who will experience an increase in cardiac output with fluid administration RCTs did not find using central venous pressure to guide fluid therapy to improve outcomes in sepsis
Urine output[40]	Volume of urine produced over a time interval	0.5-1.5 mL/kg/h	Urine output may be a surrogate measure of the perfusion of the kidney	Urine output is influenced by factors other than perfusion of the kidney, including microvascular changes and the development of acute tubular necrosis Fluid administration that increases cardiac output and organ perfusion may not increase urine output
Blood lactate levels[41,42]	Concentration of lactate in the blood	1 to 2 mmol/L	Increased lactate levels may indicate inadequate oxygen delivery from insufficient cardiac output or blood oxygen content	Elevated lactate levels in sepsis frequently occur despite adequate oxygen delivery to tissues Although decreasing lactate identifies patients likely to experience better outcomes, RCTs did not find using lactate clearance to guide resuscitation improved outcomes in sepsis
Cutaneous capillary refill time[42,43]	Time required for return of color after application of pressure to a capillary bed	≤3 s	Capillary refill time measures peripheral perfusion, reflects coupling between the macrocirculation and microcirculation, and responds rapidly to fluid resuscitation	Capillary refill time is an inexpensive and universally available test of peripheral perfusion An RCT found outcomes of sepsis to be at least as good with use of capillary refill time compared with lactate clearance to guide fluid therapy

Abbreviations: RCT, randomized clinical trial; $ScvO_2$, central venous oxygen saturation.

resuscitation phase. In the resuscitation phase, fluid therapy is typically continued until the patient's mean arterial pressure no longer increases with IV fluid administration, goals of resuscitation are attained, the patient's condition is no longer immediately life threatening, or complications of fluid therapy arise (eg, worsening hypoxemia).

Early Fluid Therapy and Early Goal-Directed Therapy

Evidence for early fluid therapy immediately after sepsis diagnosis is limited. An RCT of 3141 children (median age, 2 years) presenting with acute infection reported that, compared with no IV fluid bolus, the mortality was higher among patients randomized to receive IV fluid boluses of either 0.9% saline or albumin. Mortality rates were 12.0% with albumin, 12.2% with 0.9% saline, and 8.7% for those who received no IV fluid (P = .004).[44] An administrative data analysis reported that adherence to a 3-hour bundle of sepsis management (blood cultures, antibiotics, and lactate measurement) was associated with lower mortality (among 49 331 patients, the longer the time to complete the 3-hour bundle, the higher the in-hospital mortality; odds ratio, 1.04 per hour [95% CI, 1.02-1.05]; P < .001); however, time completion of initial fluid bolus was not associated with lower mortality (odds ratio, 1.01 per hour [95% CI, 0.99-1.02]; P = .21).[50]

Optimal fluid therapy in the resuscitation phase has been informed by RCTs to define early goal-directed therapy (EGDT). EGDT is defined by a specific approach to managing sepsis-induced hypoperfusion, which includes administering IV fluid boluses to achieve a central venous pressure of 8 to 12 mm Hg, vasopressors to achieve a mean arterial blood pressure of 65 to 90 mm Hg, and red blood cell transfusions and/or inotropes to achieve a central venous oxygen saturation of at least 70%.[32,37-39]

In an RCT of 263 patients with sepsis-induced hypoperfusion in an urban emergency department,[26] compared with a control group, EGDT reduced hospital mortality (30.5% vs 46.5%; P = .009).

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However, in an individual patient-level meta-analysis that combined results from 3 subsequent international RCTs (3723 patients in 138 hospitals) of patients who already received initial fluids, EGDT was not associated with improved 90-day mortality compared with usual care (EGDT, 24.9% vs usual care, 25.4%; *P* = .68).[51] It remains unclear whether care bundles that include fluid therapy and other sepsis interventions improve outcomes.[33,50,52,53]

An open-label RCT compared restrictive vs liberal fluid therapy among 1563 patients with sepsis-induced hypotension who had received an average of 2 L of fluid prior to enrollment.[47] In the restrictive group, hypotension was treated with vasopressors, and additional fluid was administered only for select indications. In the liberal group, hypotension was treated with fluid administration, and vasopressors were administered only for select indications. The median volume of IV fluid received in the first 24 hours was 1.2 L in the restrictive group and 3.4 L in the liberal group. All-cause mortality before discharge home by day 90 did not significantly differ between the restrictive fluid group (14.0%) and the liberal fluid group (14.9%) (*P* = .61).[47]

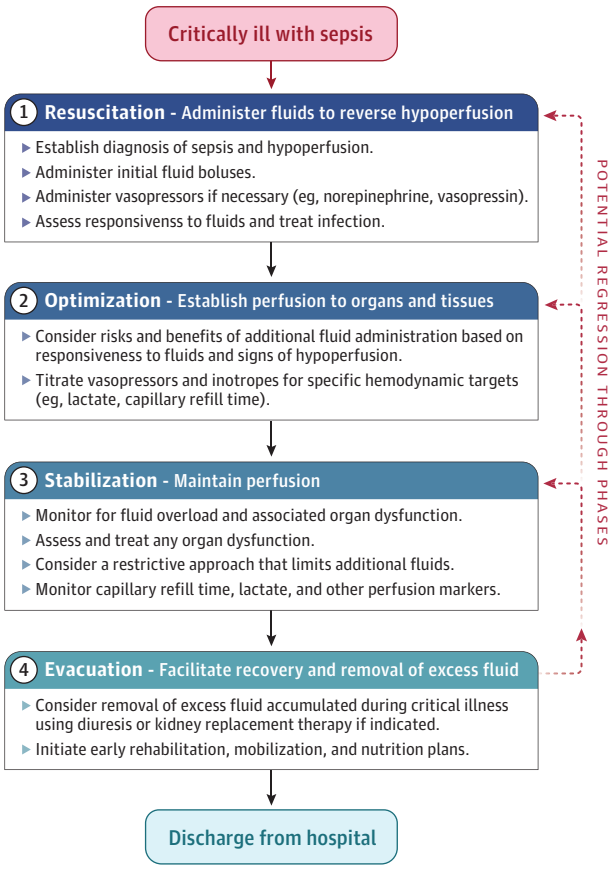
RCTs in low- and middle-income countries compared administration of IV fluid vs no fluid for acutely ill children and adults presenting with hypoperfusion from infection. An RCT of 209 adults with sepsis in Zambia reported significantly higher mortality in patients randomized to receive IV fluid vs vasopressors as part of an EGDT protocol compared with usual care (48.1% vs 33.0%) (*P* = .03).[45] An RCT of 424 patients with early septic shock in 5 countries (Argentina, Chile, Colombia, Ecuador, and Uruguay) that compared use of lactate levels vs capillary refill time to guide fluid therapy found no statistically significant difference in mortality by day 28 between the 2 groups (34.9% in the capillary refill time group vs 43.4% in the lactate clearance group (*P* = .06).[42] However, a secondary bayesian analysis suggested probable benefit for capillary refill time–guided resuscitation (odds ratio for 28-day mortality, 0.65 [95% credible interval, 0.43-0.96]; 98% probability of benefit).[43]

Together, these results suggest that, for patients with sepsis who have received 1 to 3 L of fluid, early goal-directed therapy targeting central venous pressure, mean arterial pressure, and central venous oxygen saturation may not improve outcomes and that outcomes may be similar between an approach that prioritizes additional fluid administration and one that prioritizes use of vasopressors.

Optimization and Stabilization Phases

The optimization phase has the goal of attaining perfusion to organs and tissues, and the stabilization phase has the goal of maintaining homeostasis and facilitating organ dysfunction resolution. Few RCTs have studied fluid therapy during these phases. The CLASSIC trial[46] compared restrictive vs standard fluid management following initial resuscitation in 1554 critically ill adults. Investigators hypothesized that a more restrictive approach, with fluid boluses limited to patients with markers of severe hypoperfusion, would improve 90-day mortality by avoiding unnecessary fluid accumulation. The restrictive strategy, in which fluid boluses were allowed only for lactate level above 4 mmol/L, mean arterial pressure below 50 mm Hg, mottling beyond the edge of the kneecap, or diuresis of less than 0.1 mL/kg/hour during first 2 hours after randomization, resulted in 1627 mL less IV fluid administration through day 5 of ICU admission compared with the liberal group, in which fluid was administered as long as patients experienced hemodynamic improvement. At 90-day follow-up, mortality did not differ between groups (restrictive [42.3%] vs standard [42.1%]; *P* = .96). Secondary outcomes, including kidney injury; cerebral, myocardial, intestinal, or limb ischemia; and number of days alive and out of the hospital were similar between groups. Variability between the trials in the definitions of restrictive or liberal fluid management, markers of hypoperfusion, and the indications for fluid therapy made it difficult to develop a single best approach to fluid therapy among patients with critical illness. A reasonable approach is to limit fluid administration to patients' objective markers of hypoperfusion and fluid responsiveness.[27]

Figure 2. Timing of Fluid Administration and Removal


Critically ill with sepsis
1 Resuscitation - Administer fluids to reverse hypoperfusion
Establish diagnosis of sepsis and hypoperfusion.
Administer initial fluid boluses.
Administer vasopressors if necessary (eg, norepinephrine, vasopressin).
Assess responsivenss to fluids and treat infection.
2 Optimization - Establish perfusion to organs and tissues
Consider risks and benefits of additional fluid administration based on responsiveness to fluids and signs of hypoperfusion.
Titrate vasopressors and inotropes for specific hemodynamic targets (eg, lactate, capillary refill time).
3 Stabilization - Maintain perfusion
Monitor for fluid overload and associated organ dysfunction.
Assess and treat any organ dysfunction.
Consider a restrictive approach that limits additional fluids.
Monitor capillary refill time, lactate, and other perfusion markers.
4 Evacuation - Facilitate recovery and removal of excess fluid
Consider removal of excess fluid accumulated during critical illness using diuresis or kidney replacement therapy if indicated.
Initiate early rehabilitation, mobilization, and nutrition plans.
Discharge from hospital
POTENTIAL REGRESSION THROUGH PHASES

Steps indicate fluid therapy across the conceptual phases of critical illness. Patients may progress linearly through the 4 phases or may move back and forth between phases.

Evacuation

Evacuation is the last phase of fluid therapy. Critically ill adults with sepsis may experience edema and organ failure due to excess accumulation of fluids administered during critical illness[15] and reduced capacity for fluid elimination (eg, due to acute kidney injury). Daily documentation of fluid intake, output, balance, and weights, and setting specific goals for fluid management may help clinicians prevent adverse outcomes due to fluid accumulation such as acute kidney injury, abdominal compartment syndrome, and mortality.[12,13] During recovery from critical illness, patients may spontaneously excrete excess accumulated fluid. For some patients, facilitating fluid removal

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Table 3. Summary of Randomized Clinical Trials of Fluid Therapy in Critical Illness According to Resuscitation Phases and Their Implications for Practice

Trial source by phase of therapy considered	Population and location	Setting	Hypothesis	Fluid management	Results	Implications
Resuscitation phase						
FEAST Maitland et al,[44] 2011	3141 Children with severe febrile illness	6 Centers: Kenya (1), Tanzania (1), Uganda (4)	Fluid bolus would improve 48-h mortality	Intervention 1 Administering 20 mL/kg of 0.9% saline in 1 h Intervention 2 Administering 20 mL/kg of 5% albumin in 1 h Control No bolus Additional bolus allowed in intervention groups	Higher 48-h mortality with any fluid bolus (relative risk, 1.45 [95% CI, 1.13-1.86]; P = .003) Cardiovascular collapse was the most common mortality cause	In a specific population, fluid bolus increased short term mortality
ProCESS Yealy et al,[32] 2014	1351 Patients with sepsis and hypotension refractory to ≥1000 mL of initial bolus	31 Hospitals in the United States	EGDT would improve in-hospital mortality truncated at 60 d	Intervention 1 Traditional EGDT (as in Bentzer et al[28]); fluid given in 500-mL bolus until central venous pressure is >8 mm Hg Intervention 2 500- to 1000- mL fluid bolus until systolic blood pressure is >100 mm Hg, or shock index is <0.8 or signs of fluid overload Control Fluid therapy as per clinician's discretion until signs of fluid overload	Median fluid use of 2.8 L in EGDT group, 3.3 L in modified (protocol-based) group, and 2.3 L in control group in the first 6 h Mortality was similar in protocolized groups when compared with standard of care (relative risk, 1.04 [95% CI, 0.82-1.31]; P = .83) Patients in the EGDT group were more frequently admitted to the ICU	This trial did not support EGDT or a modified EGDT approach in sepsis patients and could not confirm previous results
ProMISe Mouncey et al,[38] 2015	1260 Patients with sepsis, signs of systemic inflammatory response syndrome, and refractory hypotension to initial 1000-mL fluid boluses	56 Hospitals in England	EGDT would reduce 90-d mortality	Intervention Traditional EGDT (as in Bentzer et al[28]); fluid given in 500 mL over 20-min bolus until central venous pressure is >8 mm Hg Control Fluid therapy as per clinician's discretion until signs of fluid overload	Median fluid use of 1750 mL in EGDT group, 1500 mL in control group in the first 6 h No found differences in outcome with EGDT (relative risk, 1.01 [95% CI, 0.85-1.20]; P = .90)	This trial could not find a benefit of EGDT therapy
ARISE Peake et al,[39] 2014	1600 Patients with sepsis defined as ProCESS	51 Hospitals: Australia (42), Finland (2), Hong Kong (3), Ireland (1), New Zealand (3)	EGDT would reduce 90-d mortality	Intervention Traditional EGDT (as in Bentzer et al[28]); fluid given in 500-mL bolus until central venous pressure is >8 mm Hg or >12 mm Hg if patient is on noninvasive or invasive ventilation Control Fluid therapy as per clinician's discretion	Mean fluid use in the first 6 h was slightly higher in EGDT than control groups (1964 vs 1713 mL)	This trial did not find a clear benefit of EGDT, but all patients used fluids before enrollment

(continued)

through pharmacologic (eg, diuretics) or mechanical (eg, kidney replacement therapy) approaches may be necessary.

A clinical trial of 1000 mechanically ventilated patients with acute lung injury following initial resuscitation[48] reported that when compared with conservative fluid management, liberal fluid management increased fluid accumulation by approximately 7 L over 7 days (P < .001), but there was no significant difference in mortality between the 2 groups (conservative [25.5%] vs liberal [28.4%]; P = .30). Patients in the conservative fluid management group had more days alive (mean [SD] 14.6 [0.5] days vs 12.1 [0.5] days for the liberal group; P < .001) and were free of mechanical ventilation at 60 days, and they had more days not spent in the ICU at 60 days (13.4 [0.4] days vs 11.2 [0.4] days for the liberal group; P < .001). The GODIF trial compared furosemide titration to attain a net negative fluid balance with standard of care.[49] The clinical trial was stopped early due to imprecise fluid balance assessment, underscoring challenges in testing this scientific question. The protocol was altered, and a second phase of the trial was continued.

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Table 3. Summary of Randomized Clinical Trials of Fluid Therapy in Critical Illness According to Resuscitation Phases and Their Implications for Practice (continued)

Trial source by phase of therapy considered	Population and location	Setting	Hypothesis	Fluid management	Results	Implications
Simplified Severe Sepsis Protocol 2 Andrews et al,[45] 2017	209 Adult patients with sepsis and hypotension	1 Center in Zambia	An EGDT in a resource-constrained scenario would improve outcomes	Intervention 2.0 L Bolus in 1 h followed by additional ≤2.0 L over 4 h; fluids withheld if arterial oxygen saturation decreased by 3% or respiratory rate increased by 5 or jugular venous pressure reached 3 cm or above the sternal angle Control Usual care	Intervention group received 3.5 L (IQR, 2.7-4.0 L) vs 2.0 L (IQR, 1.0-2.5 L) in the control group Hospital mortality was higher in intervention group (relative risk, 1.46 [95% CI, 1.04-2.05]; P = .03)	A more aggressive fluid resuscitation strategy with blunt limits for fluid loading results in worse outcomes in this population
Resuscitation + optimization phases						
ANDROMEDA-SHOCK Hernández et al,[42] 2019	424 Patients with early septic shock Septic shock was defined as suspected or confirmed infection, plus hyperlactatemia (≥2.0 mmol/L) and requirements of vasopressors to maintain a mean arterial pressure of 65 mm Hg after an intravenous fluid load of ≥20 mL/kg over 60 min	26 ICUs in Argentina, Chile, Colombia, Ecuador, Uruguay	Capillary refill time–guided therapy would improve outcomes in patients with septic shock (28-d mortality)	For both groups, fluid boluses were only used if signs of preload responsiveness using dynamic parameters suggested patients were fluid responsive At least 57% of all patients were fluid responsive at enrollment; the protocol also included vasopressor and inodilator test use for some scenarios[31]	The capillary refill-guided group received 2359 mL vs 2767 mL in the control (lactate clearance) group Survival at day 28 was similar between groups (hazard ratio, 0.75 [95% CI, 0.55-1.02]; P = .06), although a bayesian reanalysis suggested a high probability of overall benefit[43]	Capillary refill time-guided therapy might be superior to lactate-guided therapy and may result in lower amounts of fluid being used
Resuscitation + optimization + stabilization phases						
CLASSIC Meyhoff et al,[46] 2022	1554 Patients with septic shock (sepsis, lactate >2 mmol/L, need for vasopressors with ≥1 L of fluid use)	31 ICUs in Belgium, the Czech Republic, Denmark, Italy, Norway, Sweden, Switzerland, United Kingdom	A restrictive fluid therapy approach would be associated with 7% lower 90-d mortality compared with standard care	Restrictive group Fluid given only if severe hypoperfusion (lactate >4 mmol/L, mean arterial pressure <50 mm Hg, mottling beyond the edge of the kneecap, diuresis of < 0.1 mL/kg/h during first 2 h after randomization was present (recommended bolus of 250-500 mL); fluids to replenish losses were allowed Standard group Fluid prescribed while patients improved with fluid challenges Fluid strategies were applied for ≤90 d after enrollment	Both groups received approximately 3 L of fluids before enrollment Median intravenous fluid use at day 5 after enrollment was 1450 mL in the restrictive vs 3077 mL in the standard group The trial had neutral results for 90-d mortality (relative risk, 1.00 [95% CI 0.89-1.13])	A restrictive strategy was not superior to a standard fluid regimen in this large multicenter trial

(continued)

Results of RCTs have been conflicting regarding kidney replacement therapy for removing excess fluid. In a 231-patient single-center RCT, mortality was lower with early kidney replacement therapy (39.3%) vs with late kidney replacement therapy (54.7%) at 90-day follow-up (P = .03).[54] In this trial, early kidney replacement therapy was defined as kidney replacement therapy initiated if urinary output was less than 0.5 mL/kg/hour for at least 12 hours or if there was a 2-fold increase in serum creatinine level compared with baseline. Late kidney replacement therapy was defined as initiating therapy only when urinary output was less than 0.3 mL/kg/hour for at least 24 hours and/or a greater than 3-fold increase in serum creatinine level compared with baseline or a serum creatinine level of greater than or equal to 4 mg/dL and/or with an acute increase of at least 0.5 mg/dL within 48 hours or urgency for kidney replacement therapy such as refractory hypervolemia or hyperkalemia among others (54.7%; P = .03 at 90-day follow-up).[54]

However, these results were not confirmed in 3 larger multicenter trials.[55-58] In the AKIKI trial (620 patients including 484

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Table 3. Summary of Randomized Clinical Trials of Fluid Therapy in Critical Illness According to Resuscitation Phases and Their Implications for Practice (continued)

Trial source by phase of therapy considered	Population and location	Setting	Hypothesis	Fluid management	Results	Implications
CLOVERS Shapiro et al,[47] 2023	1563 Patients with sepsis-induced hypotension despite receiving 1-3 L of intravenous fluid	60 Centers in the United States	A restrictive fluid therapy would be associated with lower 90-d mortality	Restrictive group Maintenance fluids discontinued, no further fluid boluses administered except for select indications, vasopressors administered for hypotension Liberal group 2 L of additional boluses were administered with use of vasopressors only if select were criteria met	Median volume of fluid in the 24 h after enrollment was 1.2 L in the conservative group and 3.4 L in the liberal group (difference, −2.1 L) Trial was halted for futility Death by day 90 did not differ between the restrictive (14.0%) and liberal (14.9%) groups No secondary outcomes differed between groups	For patients with sepsis and continued hypotension after 1-2 L of intravenous fluid, an approach that limits fluid and prioritizes vasopressors and an approach that prioritizes additional fluid administration produced similar patient outcomes
Evacuation phase						
FACTT Wiedemann et al,[48] 2006	1000 patients receiving mechanical ventilation with acute lung injury	20 Centers in the United States and Canada	A conservative fluid strategy would improve 60-d mortality	Liberal Static preload measurements (central venous pressure or pulmonary artery occlusion pressure) were kept at higher values Conservative Lower values of static preload measurements were triggers for furosemide use For both groups, furosemide was titrated to achieve intravascular pressure goals Furosemide was not used if patients were being treated with vasopressors or had poor tissue perfusion	Patients in the conservative group had a neutral fluid balance at day 7, while patients in the liberal group were on average approximately 7 L positive Mortality at day 60 was not significantly different between fluid management strategies The conservative strategy was associated with an increase in the mean (SD) number of ventilator-free days (14.6 [0.5] vs 12.1 [0.5]; $P < .001$) and ICU-free days (13.4 [0.4] vs 11.2 [0.4]; $P < .001$) There was no increase in receipt of kidney replacement therapy	This was the first trial to show an improvement in respiratory organ dysfunction with a clinically relevant end point A neutral fluid balance was achieved without an increase in other organ dysfunctions including shock or receipt of kidney replacement therapy
GODIF Wichmann et al,[49] 2023 Second version ongoing	Recruitment follows on a second protocol version; includes patients with fluid accumulation assessed by net fluid balance according to weight at the time of enrollment	First protocol version was halted after 41 patients of 1000 planned at 3 ICUs in Denmark	Furosemide will increase days alive and days outside the hospital at 90 d	Placebo vs furosemide infusion to obtain negative fluid balance toward neutralization of positive fluid balance	First version halted at 41 patients due to protocol violations due to perceived imprecision in recording of fluid balances Updated trial is enrolling patients	The second protocol version is ongoing

Abbreviations: EGDT, early goal-directed therapy; ICU, intensive care unit.

patients with sepsis), 60-day mortality was not different between early vs delayed kidney replacement treatment (48.5% vs 49.7%; $P = .79$).[55] In the IDEAL-ICU trial (488 patients with sepsis) mortality was 58% in the early-strategy group vs 54% in the delayed-strategy group at 90 days ($P = .38$).[56] In the STARRT-AKI international RCT (3019 patients with acute kidney injury of whom 57.7% had sepsis), 90-day mortality was 43.9% in the early (accelerated-strategy) group and 43.7% in the standard-strategy group ($P = .92$).[57] Kidney replacement therapy among survivors was higher in the accelerated-strategy group (10.4% vs 6.0%).

In summary, among patients without acute respiratory distress syndrome, RCTs did not support early (or accelerated) kidney replacement therapy to remove fluid. Furthermore, both slow (net ultrafiltration <1 mL/kg/hour) and rapid (net ultrafiltration >1.75 mL/kg/hour) fluid removal with kidney replacement therapy, compared with moderate-rate fluid removal (1.01-1.75 mL/kg/hour), may be associated with higher mortality and longer duration of kidney replacement therapy.[59] The optimal rate and duration of fluid removal by kidney replacement therapy during the later phases of critical illness remains unclear.

Selecting Fluid Type

IV fluid solutions may be classified as crystalloid solutions (which contain water and electrolytes) or colloid solutions (which contain water, electrolytes, and a larger compound). The most common crystalloid solutions are 0.9% sodium chloride (saline) and balanced or buffered crystalloid solutions, such as Ringer lactate.

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Crystalloid Solutions

Two classes of isotonic crystalloid solutions exist: 0.9% sodium chloride (saline) and balanced crystalloid solutions, in which chloride is replaced with a buffer such as lactate, gluconate, or acetate to prevent hyperchloremic metabolic acidosis. Multiple large, international RCTs have compared balanced solutions vs saline for fluid resuscitation in critically ill patients.[60-63] Among 2278 ICU patients in the SPLIT trial (of whom only 77 had sepsis), acute kidney injury occurred in 9.6% of patients in the balanced crystalloid group and 9.2% of patients in the 0.9% saline group (P = .77).[60] Among 15 802 critically ill adults at a single academic institution in the SMART trial,[61] rates of death, kidney replacement therapy, or persistent kidney dysfunction was 14.3% in the balanced crystalloid group vs 15.4% in the 0.9% saline group (P = .04). In a secondary analysis of the SMART trial among the 1641 patients with sepsis,[64] 30-day in-hospital mortality was 26.3% in the balanced crystalloids group and 31.2% in the 0.9% saline group (P = .01).[64] Among 10 520 critically ill adults in the BaSICS trial, there was no difference in 90-day mortality between patients randomized to receive balanced crystalloid solution (26.4%) and patients randomized to receive 0.9% saline (27.2%) (adjusted hazard ratio, 0.97 [95% CI, 0.90-1.05]), and 90-day mortality among patients with sepsis was 46.7% in the balanced crystalloids group and 49% in the saline group.[62] Among 5037 critically ill adults in the PLUS trial, there was no difference in 90-day mortality between patients in the balanced crystalloids group and patients in the 0.9% saline group (21.8% vs 22.0%; difference, −0.2 percentage points [95% CI, −3.6 to 3.3]).[63] Among patients with sepsis, mortality at 90 days was not significantly different between the balanced crystalloid and saline groups.

A meta-analysis of 34 450 patients in 6 low-risk of bias RCTs reported in a frequentist analysis that the relative risk for 90-day mortality was 0.96 (95% CI, 0.91-1.01) for balanced solutions compared with saline.[65] In bayesian analysis, the probability that balanced crystalloids decreased mortality compared with saline was 89.5%. Among 6754 patients with sepsis from 5 RCTs, there was no difference in mortality between a balanced crystalloid group and a saline group (31.3% vs 33.9%; relative risk, 0.93 [95% CI, 0.86-1.01]).[65] In a preplanned subgroup analysis (BASICS trial), balanced crystalloids increased mortality in 483 patients with traumatic brain injury (odds ratio, 1.48; 95% credible interval, 1.04-2.09).[66] It is conceivable that balanced crystalloid solutions attain outcomes that are at least as good as for saline in patients with sepsis.

Colloid Solutions

Human albumin is the most frequently used colloid in ICU settings. An RCT of 6997 critically ill patients that included 1218 patients with sepsis reported that compared with saline, albumin did not reduce mortality (20.7% for albumin vs 20.8% for saline; P = .87).[67] Results for mortality were similar in the subgroup of patients with sepsis (30.7% for albumin vs 35.3% for saline; P = .09). An RCT of 1818 ICU patients with sepsis found that mortality at 28-day follow-up was not significantly different between patients who received albumin (31.8%) compared with patients who received crystalloid solutions (32.0%) (P = .94).[68] The role of albumin in sepsis treatment, if any, is presently unclear.

In multiple RCTs, semisynthetic colloid solutions such as hydroxyethyl starch were associated with increased rates of acute kidney injury, kidney replacement therapy, and death in patients with sepsis.[69-71] In an RCT of 537 patients with sepsis, compared with crystalloid therapy (lactated Ringer), hydroxyethyl starch increased the incidence of acute kidney injury (22.8% vs 34.9%; P = .002).[69] In an RCT of 804 patients with sepsis or septic shock, compared with Ringer acetate, hydroxyethyl starch increased mortality at 90 days (51% vs 43%; P = .03).[70] In an RCT of 7000 ICU patients, compared with saline, hydroxyethyl starch significantly increased need for kidney replacement therapy (7.0% vs 5.8%; P = .04)[71]; in the subgroup of 1921 patients with sepsis in this trial, compared with saline, hydroxyethyl starch did not increase mortality (25.4% mortality for hydroxyethyl starch and 23.7% for saline; risk ratio, 1.07 [95% CI, 0.92-1.25]; P = .38).[71] In summary, hydroxyethyl starch should not be administered to patients with sepsis.

Box. Common Questions Regarding Fluid Therapy for Critically Ill Patients With Sepsis

When Should Fluid Therapy Be Considered for Patients With Sepsis?
Fluid therapy should be initiated for patients with evidence of sepsis-induced hypoperfusion (altered mental status, low arterial blood pressure, reduced urinary output, abnormal capillary refill time) who are likely to have increased cardiac output with fluid administration. Fluid administration should be discontinued when evidence of hypoperfusion resolves, the patient no longer responds to fluid, or the patient shows evidence of fluid overload.

What Type of Fluid Should Be Used?
Balanced solutions (eg, Ringer lactate, Ringer acetate, Plasma Lyte) should be selected over 0.9% saline for fluid therapy in patients with sepsis. Hydroxyethyl starches should not be used for patients with sepsis.

When Should Fluid Removal Be Considered, and How Should Fluid Be Removed?
Fluid removal should be considered after the resuscitation and optimization phases and when a patient has stabilized (eg, decreasing vasopressor doses, adequate peripheral perfusion). Diuretics are first-line therapy to facilitate elimination of fluid. Kidney replacement therapy may be considered for patients with severe acute kidney injury who have complications from fluid overload are unresponsive to diuretic therapy.

Infusion Rate

A systematic review that included 3601 patients in 85 studies reported that a rapid infusion rate (<30 minutes) was associated with higher probability of increasing stroke volume or cardiac output in response to fluid administration, likely by more effectively increasing venous return and preload.[72] The volume of fluid use was less than 500 mL in 12.7% of the trials, 500 mL in 79.4% of the studies, and more than 500 mL in 7.9% of the reports. An RCT involving 10 520 critically ill patients requiring IV fluid therapy compared infusion at a slower rate (333 mL/hour) vs a faster rate (999 mL/hour).[73] Mortality rates were 26.6% in the group that received a slower infusion and 27.0% in the faster infusion group (P = .46). In a post hoc analysis, faster infusion rates were associated with benefit in a subgroup that included patients with sepsis (odds ratio for mortality, 0.72 [95% credible interval, 0.54-0.91]; probability of benefit >0.99).[74] The effects of different infusion rates on outcomes in critically ill patients with sepsis remain unclear.[75]

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Applying Evidence, Uncertainties, and Future Directions

When treating a patient with sepsis, clinicians must evaluate benefits and risks of fluid therapy in each phase of critical illness (**Box**). Decisions regarding fluid management require consideration of the patient's acute conditions and chronic comorbidities that may influence measures of fluid responsiveness (eg, right ventricular failure) or the patient's ability to receive fluid without developing complications from fluid therapy (eg, end-stage kidney disease)[76] (Table 1). Information about the patient's condition should be integrated with evidence that informs which fluid therapies improve patient outcomes.

Based on current evidence, critically ill patients with sepsis should typically receive fluid as therapy for expansion, maintenance, or medication administration. Administration of additional IV fluid and the amount of fluid to administer should be based on medical history, physical examination, laboratory studies, and imaging along with the patient's phase of illness and measures of fluid responsiveness. Effects of fluid restriction have ranged from benefit (eg, shorter duration of ventilation in acute respiratory distress syndrome), to no effect (eg, no evidence of effect on mortality in sepsis-induced hypotension), to harm (eg, abdominal compartment syndrome). Balanced crystalloids are a reasonable initial IV fluid for patients with sepsis, but balanced crystalloids should be avoided in patients with traumatic brain injury. Hydroxyethyl starch, a semisynthetic colloid solution, should be avoided in patients with sepsis.

Limitations

This review has several limitations. First, the literature search may have missed some relevant research articles. Second, quality of included articles was not formally evaluated. Third, the trials reviewed were heterogeneous and several definitions such as *restrictive*, *liberal*, and *early* may impair interpretation of the results.

Conclusion

Fluid therapy is an important component of treating patients who are critically ill with sepsis. Although optimal fluid management in patients with sepsis remains uncertain, clinicians should consider the risks and benefits of fluid administration in each phase of critical illness, avoid use of hydroxyethyl starch, and facilitate fluid removal for patients recovering from acute respiratory distress syndrome.

ARTICLE INFORMATION

Accepted for Publication: May 7, 2023.

Conflict of Interest Disclosures: Dr Zampieri reported other from Baxter Hospitalar (provision of fluids and logistics for the BaSICS trial) during the conduct of the study; personal fees from Bactiguard (statistical consulting) and Baxter (advisory board); grants from Ionis Pharmaceuticals (to his institution for investigator initiated trials) outside the submitted work; and serving as lead investigator of the BaSICS trial. Dr Bagshaw reported personal fees (advisory board) from Baxter during the conduct of the study; personal fees from BioPorto (funding for clinical adjudication) and Novartis (advisory board) outside the submitted work; and serving as lead investigator of the STARRT-AKI trial. Dr Semler reported grants from the National Heart Lung and Blood Institute (K23HL143053) and personal fees from Baxter International (advisory board) during the conduct of the study; personal fees from Aerpio Pharmaceuticals (data safety monitoring board member) outside the submitted work; and serving as lead investigator of the SMART trial and as co-investigator of the CLOVERS trial.

Submissions: We encourage authors to submit papers for consideration as a Review. Please contact Mary McGrae McDermott, MD, at mdm608@northwestern.edu.

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